THE

AMERICAN JOURNAL

OF THE MEDICAL SCIENCES

FEBRUARY, 1915

# ORIGINAL ARTICLES

## NEW USES OF SPECIFIC SKIN TESTS IN CERTAIN OF THE INFECTIOUS DISEASES.[1]

By Frederick P. Gay, M.D.,
UNIVERSITY OF CALIFORNIA, BERKELEY, CALIFORNIA.

The expression "tuberculin reaction" suggests at once to our minds a current test of corroborative and marked value in clinical diagnosis. Whether the reaction elicited be general or local, we know that its appearance indicates that the individual has suffered or is suffering from a tuberculous lesion. We now understand that a positive tuberculin reaction in man probably indicates an active tuberculous process only when it is taken in conjunction with other clinical signs. In a similar way a positive tuberculin reaction in a cow does not of necessity mean that the animal is a menace to the milk supply, and it is only in the production of experimental herds that it is usually possible or necessary to kill off all reactors. At all events up to the present the tuberculin reaction has been used and can be interpreted only in respect to its diagnostic significance. We purpose discussing (1) the extension of local specific reactions like the tuberculin reaction to the diagnosis of other infectious diseases, and (2) certain other novel uses of these reactions which are of distinctly prognostic significance.

Koch's original interest in the administration of tuberculin in the tuberculous individual lay in its possible therapeutic value. This possibility has been realized, but only in a limited sense;

---

[1] The Samuel D. Gross Lecture of the Pathological Society of Philadelphia, October 22, 1914.

tuberculin is generally admitted to have a distinct but restricted usefulness in the cure of tuberculosis. But at the same time Koch saw and described the diagnostic uses of tuberculin. He noted the characteristic rise in temperature that follows the subcutaneous injection of tuberculin in a tuberculous animal or individual, and also the local reaction at the point of inoculation and about the tuberculous foci. But although he noted the localized reaction its diagnostic possibilities were not understood until some seventeen years later. In 1907 v. Pirquet described the simple and accurate test for tuberculosis carried out by applying tuberculin to an abrased surface of the skin (cutaneous reaction), and in the same year Calmette described an equally simple but more dangerous reaction that may be evoked in the tuberculous individual by instilling a diluted tuberculin in the conjunctival sac. These two types of localized reaction have to a large extent supplanted the generalized tuberculin test suggested by Koch.

The priority of describing a localized specific reaction in the infectious diseases of diagnostic or prognostic significance belongs, however, not to Kock or to v. Pirquet but to Edward Jenner in connection with his study of smallpox. I prefer, however, to discuss the significance of his observations in another connection.

Following the descriptions of v. Pirquet, of Calmette, and of Wolff-Eisner on the diagnostic value of localized tuberculin reactions, similar reactions have been employed in other infectious diseases. It may be mentioned categorically that the local application of the respective etiological agent has been used with more or less diagnostic success in at least hay fever, glanders, gonorrhea, leprosy, trichophytosis, sporotrichosis, and the infectious abortion of cattle. Without further discussion of these interesting results we will consider in more detail certain even more recent applications of specific localized reactions which seem to me not only of interest in themselves but indicative of a new field of usefulness.

Let us consider first the method of diagnosis proposed by Edith Claypole[2] for infections due to members of the streptothrix group of microörganisms. Dr. Claypole has found that skin tests may be employed not only to diagnose streptotrichosis differentially from tuberculosis, with which it is clinically frequently confounded, but even between members of the streptothrix group. Dr. Claypole began her work in my laboratory some three years ago with an ambitious, and I believe rather successful, attempt at a classification of the much confused group of microörganisms that may be referred to as streptotrices.[3] This group is confused not only in respect to the individuals to be included, but also in respect to priority of nomenclature. For reasons that are given in Claypole's paper it has seemed better to refer to them as streptotrices and the diseases they produce as streptotrichosis. Among the disease entities in man and animals that are produced by this group of organisms may be mentioned madura foot, actinomycosis, nocardiosis, and pseudo-tuberculosis. These diseases are, as a rule, characterized as slow, progressive, localized processes which are, however, capable of an acute general pyemic or pneumonic course. In her general comparison of the type organisms of this group, Claypole has shown that they run from mycelial, non-acid-fast forms through non-acid-fast or partially acid-fast bacillary forms to strongly acid-fast forms that are closely allied to the tubercle bacillus. Not only are these gradual transitions in type demonstrable from one species to another, but they may actually occur in the cultivation of a given species. A given organism may from time to time be more or less acid-fast and bacillary, or again at one time almost wholly mycelial and later bacillary. By means of antisera to the mycelial, to the partly acid-fast bacillary, and to the acid-fast bacillary types it was possible to show that neither extreme organism reacted with the antisera to the other extreme species, but that the intermediate partly acid-fast organism reacted with its own antiserum and with the antiserum to either extreme type. The acid-fast streptotrices, moreover, reacted with an antiserum to B. tuberculosis.

---

[2] Human Streptotrichosis and its Differentiation from Tuberculosis, Arch. Int. Med., 1914 xiv, 104.

[3] Claypole, On the Classification of the Streptotrices, Particularly on Their Relation to Bacteria, Jour. Exper. Med., 1913, xvii, 99.

In a considerable number of human cases of cervical adenitis and pulmonary disease that clinically are indistinguishable from tuberculosis some form of streptothrix has been found in pure culture. I may simply mention the names of Flexner,[4] Lubarsch,[5] Ophüls,[6] Burnet,[7] and Foulerton[8] in this connection. That a distinct though unknown percentage of glandular, pulmonary, and bone tuberculosis, so-called, is due to infection with a streptothrix is becoming evident from the work of Bridge,[9] Foulerton,[10] and Claypole. Even with the examination of discharges and sputum the diagnosis is overlooked. In the presence of a non-acid-fast streptothrix the carbolfuchsin stain results in the report of "no tubercle bacilli found." On the other hand an acid-fast streptothrix, particularly if non-mycelial, is passed as B. tuberculosis. By means of Dr. Claypole's differential skin test, streptothrix infections

[4] Pseudo tuberculosis Hominis Streptothrica, Jour. Exper. Med., 1898, iii, 435.

[5] Zur Kentniss der Strahlenpilz, Ztschr. f. Hyg., 1899, xxxi, 185.

[6] Acid-proof Bacilli in Five Cases of Pulmonary Gangrene, Jour. Med. Research, 1902, viii, 242.

[7] Streptothricee dans une adénopathie cervicale, Compt. Rend. Soc. de biol., 1913, lxxiv, 674.

[8] Streptothrix Infections, Lancet, London, 1899, ii, 779; Some Observations on a Series of Seventy-eight Cases of Streptothrix Infections, Ibid., 1913, i, 381

[9] Streptothrichosis (Actinomycosis) of the Lungs, Jour. Amer. Med. Assoc., 1911, lvii, 1501.

[10] Loc. cit.

may be readily diagnosed, and it is barely possible that when recognized they may respond to a specific treatment.

Claypole prepared solutions from two types of streptothrix, in all respects similar to old tuberculin (concentrated glycerin-bouillon growths). Her cases were all tested by the skin test of v. Pirquet with old tuberculin, with Streptotricin H. (Streptotricin Hominis, mycelial, non-acid-fast), and with Streptotricin E. (S. eppingeri bacillary, partly acid fast).

In 45 control cases which gave no clinical evidence of tuberculosis 22 reacted to old tuberculin, but none to either of the streptotricins. In 55 cases of suspected tuberculosis, comprising 42 lung, 11 gland, and 5 bone involvements, 37 reacted to tuberculin (67 per cent.); 13 of these cases reacted to Streptotricin H.; 8 to Streptotricin E., and 6 gave reactions to two of the test solutions.

Of the 13 Streptotricin H. reactions 11 were lung cases. In 9 of these no tubercle bacilli were found, but in all of them thread-like, Gram-positive organisms resembling Streptothrix H., in the 2 others, acid-fast bacilli were found as well as the mycelial organisms, and one reacted to tuberculin and one to Streptotricin E. (acid-fast), as well as to Streptotricin H. The other two positive Streptotricin H. cases were glandular; both were negative to tuberculin. In one of these cases Gram-positive segments and rods were found histologically.

Eight cases reacted to Streptotricin E., 6 with lung involvements and 2 with bone lesions; 3 of the lung cases were negative to tuberculin and had no tubercle bacilli in the sputum, without doubt infections with a less acid-fast organism than B. tuberculosis. Two of the 3 remaining cases reacted to tuberculin and to Streptotricin E. In one of these tubercle bacilli were found in the sputum. The sixth case reacted to both streptotricins and had a mycelial Gram organism and an acid-fast organism in the sputum. The bone cases did not react to tuberculin and the infections were by inference due to the Streptothrix eppingeri group of organisms.

The data from these cases should convince us that we now have a means of differential diagnosis between mycelial streptothrix infection, partly acid-fast streptothrix infections and tuberculosis. Dr. Claypole is now engaged in studying the possibilities of specific treatment in this recognizable group of streptothrix infections, in some of which vaccine treatment has already been successfully employed.

Let us next consider a form of the cutaneous reaction which is of distinct prognostic significance. Although this reaction was recognized by Edward Jenner[11] and carefully worked out by v. Pirquet[12] its significance in public health administration has,

---

[11] An Inquiry into the Causes and Effects of the Variolæ Vaccinæ, London, 1798.

[12] Allergy, Arch. Int. Med., 1911, vii, 259.

I believe, only recently been brought into prominence by Dr. Force,[13] of the Department of Hygiene in the University of California. We have already referred to Jenner as the discoverer of the skin reaction. We can do no better than quote the words he used in reporting his failure to inoculate fourteen persons who had previously been infected with cowpox with smallpox.

"It is remarkable," writes Jenner, "that variolous matter, when the system is disposed to reject it, should excite inflammation on the part to which it is applied more speedily than when it produces smallpox. Indeed it becomes almost a criterion by which we can determine whether the infection will be received or not. It seems as if a change which endures through life has been produced in the action or disposition to action in the vessels of the skin; and it is remarkable, too, that whether this change has been effected by smallpox or the cowpox that the disposition to sudden cuticular inflammation is the same on the application of variolous matter."

This "sudden cuticular inflammation" of Jenner is recognized by v. Pirquet as "the immediate reaction" which follows attempts to vaccinate those who have recovered from smallpox or have been recently vaccinated. It indicates, in other words, that protection already exists in that individual, that antibodies are present which destroy the vaccine colony and prevent the evolution of the classical vaccine pustule. Force suggests simply that this immediate reaction be looked for in twenty-four hours and that its presence is as indicative of proper vaccination as the usual pustule which appears only at the end of several days. The presence of this immunity reaction would obviate the repeated and vain attempts to produce true vaccinia in such an already protected person.

Force and Beckwith[14] have further ingenuously employed a localized reaction of this type in the differential diagnosis of smallpox. They find that rabbits may be immunized against vaccinia or variola by subcutaneous injections of vaccine virus. Such animals show a specific local reaction on the intradermal injection of vaccine virus or of pus from a smallpox vesicle. They do not, however, react to varicella material. Force has recently been able to obtain an early diagnosis in two cases of suspected smallpox by this method.

Another skin test which may come to assume prognostic value is the luetin reaction for syphilis described by Noguchi. This reaction is produced by the local application of a preparation from a pure culture of Tr. pallidum to the abrased skin. It occurs only in cases of syphilis, and particularly in those cases in which the Wassermann reaction is negative. It occurs most frequently in late tertiary cases (80 per cent.), and becomes more intense after energetic antisyphilitic treatment. According to Noguchi[15] it indicates allergy, whereas the Wassermann reaction indicates an active syphilitic process. Its author further suggests that it may well be of value in indicating those cases that will derive benefit from treatment.

---

[13] Investigation of the Causes of Failure in Cow-Pox Vaccination, Jour. Amer. Med. Assoc., 1914, lxii, 1466.

[14] Unpublished Communication through the courtesy of Dr. Force.

The Shick[16] intradermal test with diphtheria toxin, described in 1912, is of important prognostic significance. It indicates not only whether an individual has or has not diphtheria antitoxin in his blood, but very accurately whether or not he is protected from diphtheria. One-fiftieth of the minimal lethal dose of diphtheria toxin for a guinea-pig is injected intradermally in the individual to be tested. If antitoxin is present in the blood no reaction follows; if there is no antitoxin the bleb is surrounded in twenty-four to forty-eight hours by an area of redness and infiltration measuring from 1 to 2 cms., which slowly fades. It seems absolutely proved from the work of Schick and of Park and Zingher[17] that individuals who react to the irritation of the toxin have less than $\frac{1}{30}$ of a unit of antitoxin per c.c. of blood, and are not protected against diphtheria. Those who do not react are protected. The active immunity of such protected people may readily be raised by giving Behring's toxin-antitoxin vaccine. Those that give a positive reaction, the unprotected, do not respond well to active immunization and should be given antitoxin.

One of the recent interesting uses of a specific skin test is as an indication of protection against typhoid fever. The local application of extracts of the typhoid bacillus has already been tried as a diagnostic test for typhoid fever, but with indifferent success. In connection with experimental studies on methods of immunization against typhoid fever, in which my associates and I have been engaged for the past two years, many interesting questions have arisen. Dr. Claypole and I[18] have found a typhoid vaccine that produces practically no symptoms even in large doses in man, and at the same time, to judge from animal experiments, protects better than any other form of typhoid vaccine that has been described. It may simply be referred to here as the sediment of the bodies of alcohol killed, ground, sensitized typhoid bacilli from several strains. In common with many others we have found that the estimation of antibodies, particularly of the agglutinins is no measure of the degree of resistance against typhoid infection. In animals the real test of immunity is infection with the typhoid bacillus.

[15] Practical Application of the Luetin Test, New York Med. Jour., August 22, 1914.

[16] Die Diphtherietoxin-Hautreaktion des Menschens als Vorprobe der prophylaktischen Diphtherieheilseruminjektion, Münch. med. Wchnschr., 1913, lx, 2608.

[17] Active Immunization in Diphtheria Treatment by Toxin-antitoxin, Jour. Amer. Med., Assoc., 1914, lxiii, 859.

[18] An Experimental Study of Methods of Prophylactic Immunization against Typhoid Fever, Arch. Int. Med., Nov., 1914.

In the case of human beings that have been vaccinated against typhoid fever we have had no assurance that they are really protected, and still less the assurance as to how long the protection lasts. By careful tabulation of morbidity statistics we may eventually learn how long a given type of immunization protects on the average. There is no assurance, however, for the individual who may be among the unfortunate ones who have failed to respond to the treatment. Dr. Force and I[19] believe that in our typhoidin test we have found a means of indicating individual resistance to typhoid fever. We found that 41 out of 42 cases (97 per cent.), that gave a history of typhoid fever gave a positive skin reaction to a concentrated bouillon culture of B. typhosus. It may be noted that two of these positive cases had typhoid fever, forty-one and thirty-three years previously. Typhoid recoveries, it may be recalled, are to all intents thereafter protected against the disease. Repeated attacks are probably paratyphoid infections. 86 per cent. of an equal number of those that gave no history of typhoid fever gave a negative reaction. It was difficult at first to explain the 14 per cent. remaining that gave a positive test with no history of previous typhoid. We believed, as our confidence in the accuracy of the reaction grew, that these positively reacting cases may have had aborted or undiagnosed typhoid fever. This explanation is rendered probable by an observation brought to our attention by Dr. Edward von Adelung. Dr. v. Adelung was a member of a family party that visited Germany nineteen years ago. Some two weeks after they had all drunk at a suspected water source, two of the members of the party came down with a fever that ran the typical course of typhoid, and was so diagnosed. The other two had at the same time mild symptoms lasting one and three days respectively, and consisting of headache, fever, malaise and flushing, which they regarded as abortive typhoid. Neither of these latter individuals give any other history of typhoid fever. All four members give a positive typhoidin reaction.

We find that individuals that have been artificially vaccinated against typhoid give, in the majority of cases, a positive skin reaction for from one and a half to two years. It may be positive for even longer periods. There are, however, a few individuals that fail to react a few months after vaccination. This experience agrees with what we know clinically about the duration and occasional failure of typhoid immunization. We feel justified in recommending to our students that they return for a skin test a few months after vaccination and at intervals thereafter. When they fail to react they are advised to be re-vaccinated.

Our suggestion and growing belief that this skin reaction with thyphoidin is a real measure of the protection that the individual enjoys against typhoid fever is strengthened by observations on immunized rabbits. We have already shown that the agglutinin titer is no indication of the resistance of a given animal to infection, and observations on the Widal reaction in man tend to the same belief. The typhoidin reaction, on the other hand, is positive in that category of individuals that are known to be protected against typhoid fever, namely, typhoid recoveries; it does not occur in people who give no history of the disease except in a small percentage that may reasonably be suspected of having had an abortive attack. The reaction further occurs in the majority of those that have been vaccinated against typhoid within the last two years, and then gradually disappears. We had scarcely hoped to show differences in typhoidin reaction between incompletely and perfectly immunized rabbits as tested by our method of infection, which in incompletely protected animals produces carriers, but our results in this respect have exceeded our anticipations. Normal rabbits invariably give a negative intradermal typhoidin reaction. When series of rabbits are immunized, each with a different vaccine preparation, it is found that the better protected series gives a higher percentage of positive typhoidin reactions and a correspondingly smaller number of them become infected on injection of B. typhosus.

---

[19] A Skin Reaction Indicative of Immunity against Typhoid Fever, Arch. Int. Med., 1914, xiii, 471.

We have taken some interest in attempting to determine the mechanism of this typhoidin reaction. The problem was inviting since so many explanations as to the cause of the tuberculin reaction have been offered. It is perhaps most generally accepted as being due to some reaction that takes place between an antigen (tuberculin) and antibodies that have been formed in the tuberculous animal. One of the disputes is as to whether the antibodies that react are concentrated in cells or circulate in the body. It has been very difficult to prove the circulating hypothesis, as the susceptibility to tuberculin has been successfully transferred by the blood to another animal in very few instances. This passive transfer has been easy to demonstrate in rabbits immunized against the typhoid bacillus. When such an animal's serum is transfused into a normal rabbit the latter becomes susceptible to the typhoidin reaction, whereas the immunized animal when transfused with normal blood loses its susceptibility. Another interesting proof of the antigen-antibody nature of the typhoidin reaction has been by the intradermal injections of sensitized (treated with immune serum) and of unsensitized typhoid vaccines in human beings. The sensitized vaccine, although it gives no untoward symptoms when used for immunization, does produce an intradermal induration and areola, the untreated vaccine does not.

In running thus hurriedly over recent applications of specific local tests I have endeavored to show that in streptotrichosis the method serves to differentiate closely related infections, and in the case of rabbits immunized against vaccine virus it may be used indirectly to diagnose human smallpox. In the case of the Schick reaction with diphtheria toxin and the typhoidin reaction of Gay and Force, local tests indicate protection or lack of protection against the disease in question, and therefore indicate when immunization is necessary. The accelerated vaccine reaction of Jenner and v. Pirquet becomes of value as indicating protection against smallpox and the fruitlessness of further attempts at producing vaccinia.

These latter prognostic applications of localized specific reactions open up, I believe, a new field of usefulness for tests of this sort.

---

# ON THE INDICATIONS FOR ARTIFICIAL NUTRITION.

By Max Einhorn, M.D.,

PROFESSOR OF MEDICINE AT THE NEW YORK POST-GRADUATE MEDICAL SCHOOL.

Artificial or extrabuccal nutrition is frequently resorted to in our medical practice. As is well known, we possess four different methods of artificial nutrition, namely: (1) subcutaneous alimentation; (2) esophagogastral alimentation; (3) duodenal alimentation; (4) rectal alimentation.

It appears of interest to broach the subject of artificial nutrition with regard to its indications and also the special methods best suited.

With this object in view, cases in which artificial nutrition may be required can be divided into three groups:

1. Cases of subnutrition in which the digestive canal presents no obstacles to the passage of food.
2. Cases of difficult or impossible nutrition caused by obstacles to the passage of food along the digestive tube.
3. Cases in which absolute rest of certain portions of the digestive tract is imperative in order to effect a cure.

It will be best to discuss the above subject in each group separately.

Group I. *Subnutrition with a Free Food Passage Along the Digestive Canal.* Subnutrition or insufficient nutrition can be observed in almost all acute and most chronic diseases. Ordinarily, however, the physician, by rational instructions and an appropriate selection of foods, succeeds in introducing by the usual way (per os) an amount of aliment sufficient for the special case.

In rare cases the introduction of an adequate amount of food becomes difficult—if not entirely impossible—by a pronounced lack of appetite or marked aversion for food. But even then the usual mode of nutrition is persisted in, provided the difficulty